PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Tölö, Hannele	Conf.:	4589
Serial No.:	09/701,031	Group:	1646
Filed:	November 22, 2000	Examiner:	Janet L Andres
For:	METHOD FOR PREPARING VIRUS-SAFE PHARMACEUTICAL COMPOSITION		

DECLARATION SUBMITTED UNDER 37 C.F.R. 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

October 15, 2002

Sir:

I, Jaakko Veikko PARKKINEN, of the Finnish Red Cross Blood Transfusion Service, Helsinki, Finland, do hereby declare the following:

I hold the degrees of Doctor of Medicine (M.D.) and Doctor of Philosophy (Ph.D.), both from the University of Helsinki. I currently hold the position of Scientific Director of Finnish Red Cross Blood Transfusion Service, Helsinki, Finland. My Curriculum Vitae is enclosed as Appendix A.

I am one of the inventors of U.S. Patent Application No. 09/701,031.

I have read and understood the subject matter of the Advisory Action of September 17, 2002.

The following comments are offered in support of the patentability of the instant invention:

The invention relates to the preparation of virus-safe pharmaceutical compositions of biologically active proteins. In the prior art, albumin has been added to solutions of biologically active proteins to prevent loss and improve stability of the proteins during processing and storage. According to the present invention, instead of albumin, a non-ionic detergent is used. In connection with the invention, we found that detergents are statistically more effective than albumin in preventing protein loss during **virus removal filtration**. Therefore, by replacing albumin with a non-ionic detergent before virus-removal filtration, filter clogging can be prevented and protein recovery improved. Experimentally, the improvement of protein recovery has been greater than 10 %.

These results are also presented in Table I of the pending application. Even if only one pair of experiments is given in the description, the recovery was **statistically significantly** higher for detergents than for albumin, which becomes particularly apparent when further experiments are statistically analyzed ($p<0.05$, t test). More comprehensive data on experiments carried out before the priority date are therefore presented in the enclosed document titled "Statistical calculations" (Appendix B).

Appendix B discloses the results obtained for virus removal filtration of solutions containing IFN-alfa and a detergent (Tween 80) or albumin. It contains four comparative tests carried out with albumin and three tests carried out with Tween 80, including one test, which is disclosed in the pending application. The three experiments show that, compared to the use of albumin, a non-ionic detergent added before virus-removal filtration gave a 12 to 14 % higher protein recovery. This difference was statistically significant as the t test shows, $p<0.05$, and **does not reflect a biochemical error**.

Improvement of protein recovery by 12 – 14 % is important in terms of industrial exploitation of the present application. To use interferons as an example: the batch size in the production may be e.g. 1 g of pure interferon protein, which corresponds to 200,000 Mill IU. An improvement of yield already by 10 % means an additional yield of 20,000 Mill IU interferon, which has a commercial value of about 100,000 USD.

Furthermore, during virus filtration, the flux through the filter was statistically faster at the end of filtration in the presence of detergents than with albumin ($p<0.05$, t test, data shown

at the end of Appendix B). In fact, at least ten times more of interferon-containing solution could be filtered with the same filter membrane area in the presence of detergents than by using albumin. Because virus removal filters are very costly – one industrial size Planova 15N cartridge costs, at today's prices, some 4,000 USD, and can only be used once – industrial exploitation of the present application brings considerable economical benefits.

As mentioned above, the non-ionic detergent is, according to the present invention, a part of the pharmaceutical composition. By contrast, in the examples of US Patent No. 4,732,683 (Georgiades et al.), Triton X-100 is used. Triton X-100 has considerable toxicity and must be removed later in the process. Triton X-100 cannot be used for the purpose of the present application, in which non-ionic detergents with a low toxicity are added to a solution of purified biologically active protein before virus removal filtration and the following sterile filtration. According to the present application, the detergent remains in the final injectable formulation, in which it enhances the stability of the finished product.

The present invention provides a pharmaceutical composition with improved viral safety. In particular, it provides improved safety against chemically resistant viruses and prions.

In US Patent No. 4,732,683 (Georgiades et al.), it is suggested that detergents can be used in combination with ultrafiltration for removing viruses. However, the only data demonstrating virus inactivation or removal is provided in Table 7 of Example 10. This data shows that infectious *Sendai* virus is **inactivated** by the detergent used (Triton X-100). No virus **removal** by the ultrafiltration is demonstrated as there was no infectious virus left before ultrafiltration.

It should be emphasized that the detergents disclosed in the '683 reference inactivate enveloped viruses **but have no effect on physico-chemically resistant viruses, such as parvoviruses**. In the present invention, viruses including parvoviruses are removed by virus-removal filtration (nanofiltration) through a filter having a pore size of 10 to 40 nm. The detergents used in the invention are pharmaceutically acceptable and they are added for preventing loss of sticky proteins and preventing clogging of the membrane when the protein-containing solutions are filtered through a virus removal filter. Thus, in the present invention, the detergents do not achieve virus removal, but they make the filtration of biologically active proteins through virus removal filters much more efficient. Addition of detergents to the solution before virus removal filtration prevents filter clogging and improves protein recovery.

Virus removal filtration is taught in US Patent No. '315. In that reference there is no suggestion that detergents used as stabilizers in a pharmaceutical composition comprising the effluent of the filtration would prevent protein losses or clogging of the filter during filtration.

The undersigned hereby declares that all statements made herein are based upon knowledge are true, and that all statements based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: October 15, 2002

Jaakko PARKKINEN

Statistical calculations:

Virus removal filtration of IFN-alfa containing solution in the presence of a detergent (Tween 80) or albumin

The solutions indicated were filtered through a Planova 15 N filter (10 cm^2) at room temperature.
Solution flux through the membrane was monitored continuously and the ratio between the flux at the end and start was calculated.
Ratio <1,0 indicates clogging of the filter membrane during filtration.
Recovery of IFN-alfa was determined by a fluoroimmunoassay measuring native IFN-alfa.

Code of experiment	Date of experiment	Solution	Volume (ml)	Pressure (bar)	Flux at the end (ratio end/start)	Recovery of IFN-alfa (%)
		A:				
S5880	26.10.1994	IFN-alfa 0.4 M IU/ml, albumin 2 g/l, Na-PBS pH 7.3	20	0,5	0,44	90
Z015B	17.4.1997	IFN-alfa 5.0 M IU/ml, albumin 0.5 g/l, Na-PBS pH 7.3	20	0,9	0,77	90
Z017A	22.10.1997	IFN-alfa 4.3 M IU/ml, albumin 1.2 g/l, Na-PBS pH 7.0	20	0,8	0,20	89
Z019A	9.12.1997	IFN-alfa 5.0 M IU/ml, albumin 1.0 g/l, Na-PBS pH 7.0	20	0,4	0,45	95
		mean		0,65	0,47	91
		B:				
Z017B	27.10.1997	IFN-alfa 4.8 M IU/ml, Tween 80 0.2 g/l, Na-PBS pH 7.0	20	0,8	1,00	95
Z018A	25.11.1997	IFN-alfa 5.0 M IU/ml, Tween 80 0.2 g/l, Na-PBS pH 7.0	20	0,4	1,00	110
Z018B	27.11.1997	IFN-alfa 5.0 M IU/ml, Tween 80 0.2 g/l, Na-PBS pH 7.0	20	0,8	1,00	112
		mean		0,67	1,00	106
					p<0.05*	p<0.05**

*Statistical comparison of flux at the end of filtration in the presence of albumin and Tween 80

Unpaired t test

Mean flux ratio with albumin = 0,465
Mean flux ratio with detergent = 1

Assuming equal variances
Combined standard error = 0,138365
df = 5
t = 3,866572
One sided P = 0,0059
Two sided P = 0,0118

95% confidence interval for difference between means = -0,89068 to -0,17932

Assuming unequal variances
Combined standard error = 0,11694
df = 3
t(d) = 4,57499
One sided P = 0,0096
Two sided P = 0,0196

95% confidence interval for difference between means = -0,835604 to -0,234396

Comparison of variances
TWO SIDED F TEST IS SIGNIFICANT
USE APPROXIMATE t (UNEQUAL VARIANCES) RESULT

**Statistical comparison of IFN-alfa recovery in filtration in the presence of albumin and Tween 80

Unpaired t test

Mean IFN-alfa recovery with albumin = 91
Mean IFN-alfa recovery with detergent = 105,666667

Assuming equal variances
Combined standard error = 4,765618
df = 5
t = 3,0776
One sided P = 0,0138
Two sided P = 0,0276

95% confidence interval for difference between means = -26,917077 to -2,416257

Comparison of variances
Two sided F test is not significant
No need to assume unequal variances

CURRICULUM VITAE

NAME	Jaakko Veikko Parkkinen
DATE OF BIRTH	1 March 1957
CIVIL STATUS	Married to Helena Parkkinen on 20 August 1983, 3 children
NATIONALITY	Finnish
CURRENT POSITION	Scientific Director, Finnish Red Cross Blood Transfusion Service, Helsinki, Finland

EDUCATION

Doctor of Medicine (M.D.)	30 June 1982	University of Helsinki
Doctor of Philosophy (Ph.D.)	4 September 1984	University of Helsinki
Appointed Docent in Medical Chemistry	20 March 1991	University of Helsinki
Specialist in Laboratory Medicine	6 August 1991	University of Helsinki

PAST POSITIONS

Temporary Assistant and Assistant, 1978-1984
Department of Medical Chemistry, University of Helsinki
Postdoctoral Fellow 1984-1985
Biocenter, University of Basle, Switzerland
Assistant and Senior Lecturer, 1985-1986
Department of Medical Chemistry, University of Helsinki
Assistant Physician and Senior Physician Locum Tenens, 1987-1990
Clinical Laboratory, Helsinki University Central Hospital
Assistant Physician and Senior Physician Locum Tenens, 1991
Department of Rheumatology, Kivelä Hospital, Helsinki
Senior Lecturer (Associate Professor), Molecular and Cellular Biology, 1991-1993 (5-year term)
Department of Medical Chemistry, University of Helsinki
Head of Department of Plasma Product Development, 1993-1994
Finnish Red Cross Blood Transfusion Service
Head of Department of Research and Development, 1994-1998
Finnish Red Cross Blood Transfusion Service

TRAINING IN PHARMACEUTICAL PRODUCT DEVELOPMENT

Validation Issues in Chromatographic Processes
Pharmacia European Consultancy, Helsinki, Feb 1-3, 1994
Acceptance Criteria for Virus Validation Studies on Biotechnology/Pharmacy
Workshop of the ad hoc working party of CPMP, Paul Ehrlich Institut, Nov 10, 1994
Kliiniset lääketutkimukset/Clinical Trials: Principles and Practice
Lääkehuollon täydennyskoulutuskeskus, Helsinki, Jan 26-27, 1995

Stability Testing of Pharmaceuticals and Biotechnology Products
European Continuing Education College, Barcelona, April 7, 1995
Quality Assurance and GMP in Product Development and Clinical Trials Supply
David Begg Associates, York, April 24-28, 1995
Registration and Virological Aspects of Biological Medicinal Product
Management Forum Ltd, London, April 28, 1995
Kliinisen biostatistiikan peruskurssi
Suomen Astra Oy, Kirkkonummi, Nov 16-17, 1995
Kliiniset lääketutkimukset 1995 (Clinical Trials 1995)
University of Helsinki and the Finnish Society for Clinical Pharmacology, Helsinki, Nov 22-24,1995
Myyntilupaseminaari 1995
Lääkehuollon täydennyskoulutuskeskus, Helsinki, Nov 27-28, 1995
Biotechnology: Quality Control Preparation for the PLA and Pre-Approval FDA Inspection
PDA workshop, Wien, Feb 22-23, 1996
Bioseparation and Bioprocessing of Biological Molecules
University of Cambridge, Sept 30-Nov 2, 1996
International Negotiation Skills
Oy Langdons Ltd, Helsinki University of Technology, Espoo, March 6-7, 1997
Patentit hallintaan (Managing Patents)
Helsinki University of Technology, Espoo, Sept 3-4, 1997
Laatuseminaari: Tuotekehitys kilpailutekijänä
Finnish Association of Pharmaceutical Industry, Tuusula, May 15-16, 1997
Management of International R&D Projects
Helsinki University of Technology, March 10 - May 7, 1998
Compliance Seminar
Pharmaceutical Compliance Associates, Helsinki, April 29, 1998
Käytännön Farmakokinetiikka
University of Helsinki, May 14-15, 1998
Workshop on Application to Pharmaceuticals of Assays for Markers of TSE
EMEA Offices, London, Jan 19-20, 1999
Scientific writing in English
Fennomed, Helsinki, Sept 7, 1999
Terveystalousselvitys – teoriasta käytäntöön
Lääketietokeskus, Espoo, Nov 11-12, 1999
Bioteknologian ja lääkealan keksintöjen suojaaminen ja hyödyntäminen
AEL, Rantasipi Congress & Business Center, Vantaa, Feb 1-2, 2000
Tilastolliset menetelmät kliinisessä lääketieteessä – syventävä kurssi
Suomen lääkäriliitto, Helsinki, March 22, 2000
Myyntilupahakemuksen farmakologinen osio
Lääkehuollon täydennyskoulutuskeskus, Espoo, Sept 27, 2000
Elektroninen dokumentaatio
Lääkehuollon täydennyskoulutuskeskus, Espoo, Oct 8, 2001

INVITED SPEAKER IN PROFESSIONAL CONGRESSES AND TRAINING COURSES

Detection and Prevention of Transfusion-Transmitted Infections
European School of Transfusion Medicine, Pärnu (Estonia), Sept 12-15, 1998
Innovations in Biotechnology - From Discovery to Product
Helsinki Graduate School of Biotechnology and Molecular Biology, Helsinki, Dec 3-4, 1998

Biotech Alternatives to Blood and Plasma Products
IIR Conference, London, Jan 25-26, 1999
Plasma Product Biotechnology Meeting, Queensland, Australia, 1999
Plasma Product Biotechnology Meeting, Malta, 2001
AEL Insko-seminaari Kalvoerotustekniikat, Hämeenlinna, Sept 27-28, 2001
AEL Insko-seminaari Validoinnin perusteet, Helsinki, Nov 22-23, 2001
AEL Insko-seminaari Validoinnin perusteet, Vantaa, May, 2002
27th Conference of the International Society of Blood Transfusion (ISBT), Vancouver, Aug, 2002

PATENTS GRANTED

1. Parkkinen J, von Bonsdorf L: Farmaseuttiset valmisteet, FI 104466 B, 15.02.2000
2. Tölö H, Kauppinen H-L, Parkkinen J, Alm G: Menetelmä multikomponentti alfa-interferonin valmistamiseksi, FI 105319 B, 31.07.2000.
3. Tölö H, Parkkinen J: Menetelmä virusturvallisten farmaseuttisten koostumusten valmistamiseksi, FI 106465 B, 15.02.2001.
4. Parkkinen J, von Bonsdorf L : Pharmaceutical preparations, US Pat. 6,251,860, 26.06.2001
5. Parkkinen J: Treatment of plasma. EP 762893, 12.09.2001
6. Parkkinen J, von Bonsdorf L : Pharmaceutical preparations, US Pat. 6,326,473

SCIENTIFIC ACTIVITIES

Speaker in Scientific Meetings:
7th International Symposium on Glycoconjugates, Lund-Ronneby, 1982
8th International Symposium on Glycoconjugates, Houston, Texas, 1985
16th Linderstrøm-Lang Conference: Glycoconjugates in Cell Interactions, Helsinki, 1986
International Congress on Plasminogen Activators, Florence, 1990
FEMS Symposium: Molecular Recognition in Host-Parasite Interactions, Porvoo, 1991
7th International Conference of the International Society of Differentiation, Helsinki, 1992
Faculty Opponent:
Department of Physiological Chemistry, University of Gothenburg, 1988
Member of Scientific Boards and Public International Research Groups:
General Secretary, FEBS Special Meeting on Biological Membranes, Helsinki, 1994
EU Biomed II CRAFT project on the Assessment and Improvement of Selected Technologies to Remove or Inactivate TSE-Causing Agents, 1.12.1998-30.11.2000
Council of Europe Co-ordinated Research Study on Pathogen Inactivation of Labile Blood Products, 1999-2000

LIST OF SCIENTITIC PUBLICATIONS

Original Publications:

1. Renlund M, Chester A, Lundblad A, Parkkinen J and Krusius T: Free N-acetylneuraminic acid in tissues in Salla disease and the enzymes involved in its metabolism. Eur J Biochem 130: 39-45, 1983.
2. Parkkinen J, Finne J, Achtman M, Väisänen V and Korhonen T K: *Escherichia coli* strains binding neuraminyl□2-3galactosides. Biophys Biochem Res Commun 111: 456-461, 1983.
3. Parkkinen J and Finne J: Isolation and structural characterization of five major

sialyloligosaccharides and a sialylglycopeptide from normal human urine. Eur J Biochem 136: 355-361, 1983.

4. Parkkinen J: Characterization of a *scyllo*-inositol-containing sialyloligosaccharide from normal human urine. FEBS Lett 163: 10-13, 1983.
5. Parkkinen J and Finne J: Isolation and structural characterization of novel phosphate-containing sialyloligosaccharides from normal human urine. Eur J Biochem 140: 427-431, 1984.
6. Korhonen T K, Väisänen-Rhen V, Rhen M, Pere A, Parkkinen J and Finne J: *Escherichia coli* fimbriae recognizing sialyl galactosides. J Bacteriol 159: 762-766, 1984.
7. Korhonen T K, Valtonen M V, Parkkinen J, Väisänen-Rhen V, Finne J, Ørskov F, Ørskov I, Svenson S B and Mäkelä P H: Serotypes, hemolysin production, and receptor recognition of *Escherichia coli* strains associated with neonatal sepsis and meningitis. Infect Immun 48: 486-491, 1985.
8. Vauhkonen M, Viitala J, Parkkinen J and Rauvala H: High-mannose structure of apolipoprotein-B from low-density lipoproteins of human plasma. Eur J Biochem 152: 43-50, 1985.
9. Niemelä O, Risteli L, Parkkinen J and Risteli J: Purification and characterization of the aminoterminal propeptide of human type III procollagen. Biochem J 232: 145-150, 1985.
10. Parkkinen J and Finne J: Occurrence of N-acetylglucosamine 6-phospahate in complex carbohydrates: Characterization of a phosphorylated sialyloligosaccharide from bovine colostrum. J Biol Chem 260: 10971-10975, 1985.
11. Parkkinen J, Rogers G N, Korhonen T K, Dahr W and Finne J: Identification of the O-linked sialyloligosaccharides of glycophorin A as the erythrocyte receptors of S-fimbriated *Escherichia coli*. Infect Immun 54: 37-42, 1986.
12. Korhonen T K, Parkkinen J, Hacker J, Finne J, Pere A, Rhen M and Holthöfer H: Binding of *Escherichia coli* S fimbriae to human kidney epithelium. Infect Immun 54: 322-327, 1986
13. Parkkinen J, Korhonen T K, Pere A, Hacker J and Soinila S: Binding sites in the rat brain for *Escherichia coli* S fimbriae associated with neonatal meningitis. J Clin Invest 81: 860-865, 1988.
14. Korhonen T K, Haahtela K, Pirkola A and Parkkinen J: A N-acetyllactosamine-specific cell-binding activity in a plant pathogen, *Erwinia rhapontici*. FEBS Lett 236: 163-166, 1988.
15. Parkkinen J, Virkola R and Korhonen T K: Identification of factors in human urine that inhibit the binding of *Escherichia coli* adhesins. Infect Immun 56: 2623-2630, 1988.
16. Virkola R, Westerlund B, Holthöfer H, Parkkinen J, Kekomäki M and Korhonen T K: Binding characteristics of *Escherichia coli* adhesins in human urinary bladder. Infect Immun 56: 2615-1622, 1988.
17. Parkkinen J and Oksanen U: A lectin-immunofluorometric assay using an immobilized *Bandeiraea simplicifolia II* lectin for the determination of galactosylation variants of glycoproteins. Anal Biochem 177: 383-387, 1989.
18. Parkkinen J, Ristimäki A and Westerlund B: Binding of *Escherichia coli* S fimbriae to cultured human endothelial cells. Infect Immun 57: 2256-2259, 1989.
19. Parkkinen J and Korhonen T K: Binding of plasminogen to *Escherichia coli* adhesion proteins. FEBS Lett 250: 437-440, 1989.
20. Parkkinen J: Aberrant lectin-binding activity of immunoglobulin G in serum from rheumatoid arthritis patients. Clin Chem 35: 1638-1643, 1989.
21. Parkkinen J, Hacker J and Korhonen T K: Enhancement of tissue plasminogen activator-catalyzed plasminogen activation by *Escherichia coli* S fimbriae associated with neonatal septicaemia and meningitis. Thromb Haemost 65: 483-486, 1991.
22. Parkkinen J and Rauvala H: Interactions of plasminogen and tissue plasminogen activator (t-PA) with amphoterin: Enhancement of t-PA-catalyzed plasminogen activation by amphoterin. J Biol Chem 266: 16730-16735, 1991.

23. Parkkinen J, Raulo E, Merenmies J, Nolo R, Kajander O, Baumann M and Rauvala H: Amphoterin, the 30-kDa protein in a family of HMG1-type polypeptides: Enhanced expression in transformed cells, leading edge localization and interactions with plasminogen activation. J Biol Chem 268: 19726-19738, 1993.
24. Virkola R, Parkkinen J, Hacker J and Korhonen T K: Sialyloligosaccharide chains of laminin as an extracellular matrix target for S fimbriae of *Escherichia coli*. Infect Immun 61: 4480-4484, 1993.
25. Parkkinen J, Vääränen O and Vahtera E: Plasma ascorbate protects coagulation factors against photooxidation. Thromb Haemost 75: 292-297, 1996.
26. Nyman T, Tölö H, Parkkinen J and Kalkkinen N: Identification of nine interferon-α subtypes produced by Sendai virus induced human peripheral blood leukocytes. Biochem J 329: 295-302, 1998.
27. Fellman V, von Bonsdorff L and Parkkinen J: Exogenous apotransferrin and exchange transfusions in hereditary iron overload disease. Pediatrics 105: 398-401, 2000.
28. Parkkinen J, von Bonsdorff L, Peltonen S, Grönhagen-Riska C and Rosenlöf K: Catalytically active iron and bacterial growth in serum of haemodialysis patients after i.v. iron-saccharate administration. Nephrol Dial Transplant, 15: 000-000, 2000.
29. Rouhiainen A, Imai S, Rauvala H and Parkkinen J: Occurrence of amphoterin (HMG1) as an endogenous protein of human platelets that is exported to the cell surface upon platelet activation. Thromb Haemost, 84: 1087-1094, 2000.
30. Matinaho S, von Bonsdorff L, Rouhiainen A, Lönnroth M and Parkkinen J: Dependence of *Staphylococcus epidermidis* on non-transferrin-bound iron for growth. FEMS Microbiol Lett 196: 177-82, 2001.
31. Sahlstedt L, Ebeling F, von Bonsdorff L, Parkkinen J and Ruutu T: Non-transferrin-bound iron during allogeneic stem cell transplantation. Br J Haematol 113: 836-838, 2001.
32. von Bonsdorff L, Tölö H, Lindeberg E, Nyman T and Parkkinen J: Development of a pharmaceutical apotransferrin product for iron binding therapy. Biologicals 29: 27-37, 2001.
33. Tölö H, Kauppinen H-L, Alm G, Lindeberg E, Wahlstedt-Fröberg V and Parkkinen J: Development of a highly purified multicomponent leukocyte interferon-α product. J Interferon Cytokine Res, 21: 913-921, 2001.
34. von Bonsdorff L, Lindeberg E, Sahlstedt L, Lehto J and Parkkinen J: Bleomycin-detectable iron assay for non-transferrin-bound iron in hematologic maligancies. Clin Chem 48: 307-314, 2002.
35. Sahlstedt L, von Bonsdorff L, Ebeling F, Ruutu T and Parkkinen J: Effective binding of free iron by a single intravenous dose of human apotransferrin in haematological stem cell transplant patients. Br J Haematol, in press 2002.
36. von Bonsdorff L, Sahlstedt L, Ebeling F, Ruutu T and Parkkinen J: Apotransferrin administration prevents the growth of Staphyloccous epidermidis in serum by binding free iron. Submitted.
37. Sahlstedt L, Juvonen E, Ruutu T, von Bonsdorff L, Ebeling F and Parkkinen J: Prevention of catalytically active iron by apotransferrin infusions promotes hematopoietic recovery after stem cell transplantation. In preparation
38. Isoniemi H, von Bonsdorff L, Höckerstedt K and Parkkinen J: Non-transferrin-bound iron in fulminant acute liver failure. In preparation.

Invited Scientific Reviews:

1. Parkkinen J and Finne J: Isolation of sialyloligosaccharides and sialyloligosaccharide phosphates from bovine colostrum and human urine. Methods Enzymol 138: 289-300, 1987.
2. Korhonen T K, Virkola R, Westerlund B, Holthöfer H and Parkkinen J: Tissue tropism of

Escherichia coli adhesins in human extraintestinal infections, Current Topics in Microbiology 151: 115-127, 1990.

3. Parkkinen J: *Escherichia coli* S fimbriae: oligosaccharide-specific binding to host tissues and enhancement of plasminogen activation, in Molecular Recognition in Host-Parasite Interactions: Mechanisms in Viral, Bacterial and Parasite Infections, Korhonen TK, Hovi T and Mäkelä PH, eds, Plenum publishing Co. 1992.
4. Rauvala H, Merenmies J, Raulo E and Parkkinen J: The lysine cluster proteins amphoterin and HB-GAM (heparin-binding growth-associated molecule). Trends Glycosci Glycotechnol 4: 513-523, 1992.
5. Parkkinen J: Mechanisms leading to the activation of the fibrinolytic system in septicaemia, in Fibrinolysis in Disease, Glas-Greenwalt P et al, eds, CRC Press, 1996.
6. Parkkinen J: Molecular basis of tissue tropism of bacterial meningitis, in An Introduction to Blood-Brain Barrier: Methodology and Biology, Pardridge WM, ed, Cambridge University Press, 1998.
7. Parkkinen J: Current viral safety of plasma products. Detection and Prevention of Transfusion-Transmitted infections. Proceedings of the ESTM residential course, ed. by Barbara JAJ, Sultsman M-K, Rossi U, ESTM, 1998.
8. Parkkinen J: Viral inactivation procedures of blood components. Detection and Prevention of Transfusion-Transmitted infections. Proceedings of the ESTM residential course, ed. by Barbara JAJ, Sultsman M-K, Rossi U, ESTM, 1998.
9. Bopp MKF, Morell A, Indrak K, Parkkinen J, Mertens H, Morh H, Colamartino P, Stanescu I, Oyonarte S, Delaney FM, Padilla A: Pathogen inactivation of labile blood products. Transfusion Medicine 11, 149-175, 2001. (Council of Europe study group. Pathogen inactivation of labile blood products, Council of Europe Publishing, 2000).